the treatment of all recited ocular disorders, or the use of spasmolytic peptide (SP) or pS2. Applicants respectfully disagree.

The Examiner asserts that, while enabling for a method of enhancing corneal epithelial wound healing, the specification is not enabling for treatment of all eye disorders including keratitis, keratoconjunctivitis, ophthalmic herpes zoster, ocular inflammation, or cicatricial penhigoid. In support of this rejection, the Examiner focuses on the inflammatory component of these disorders and argues that trefoil peptides do not demonstrate marked and consistent anti-inflammatory effects.

Applicant notes that the symptoms of these disorders cannot be characterized simply as inflammatory reactions. Each of the recited conditions results in a disruption or loss of corneal or conjunctival epithelial integrity, rendering the eye more susceptible to further infection or damage which could ultimately result in scarring and a loss of vision. The methods of this invention are primarily directed toward maintaining epithelial viability and integrity. Any anti-inflammatory effect that trefoil peptides may exert are obviously beneficial, but not central to the desired therapeutic effect. The Examiner is directed to the experiments presented in Example 12 (pages 41-45) and specifically Figure 11. Here Applicant demonstrates the that the trefoil peptides, ITF and hSP, can promote migration of corneal epithelial cells across areas of damage. These effects do not depend on modulating an inflammatory response. Applicant also notes that claims 1 and 7 have been amended to limit the use of trefoil peptides to conditions in which epithelial injury occurs.

Turning to the enablement of the family of trefoil peptides, including ITF, SP, and pS2, the Examiner incorrectly states that, "the specification is devoid of any teaching of an effect of spasmolytic peptide (SP) or pS2 on corneal wound healing" (Office Action; page 3, fifth line from bottom). Applicant notes that the results of the experiment described in Example 12, depicted in Figure 11, demonstrate that human SP is equipotent to human ITF for promoting epithelial restitution and corneal wound healing. ITF and

hSP concentrations were 0.1-1.0 $\mu g/\mu l$ in the culture media. These results were confirmed in a second experiment described in Figure 12. Thus, clear and convincing data are presented demonstrating the efficacy for two of the three claimed trefoil peptide family members.

The effect of epithelial restoration and corneal wound healing may be imputed to all trefoil peptide family members, based on a combination of the data presented in the specification and the prior art. As described above, Applicant has demonstrated that ITF and SP are effective treatments for injuries to the corneal epithelium. The prior art shows that trefoil peptide family members, particularly ITF, SP, and pS2, exhibit common function in a variety of assays which measure the effects of the trefoil peptides on other types of epithelial cells, particularly the intestinal epithelium. See, for example, Sands *et al.*, Annu. Rev. Physiol. 58:253-273, 1996 (art of record). Therefore, it is reasonable to assume that the restorative effects demonstrated for ITF and SP are common to all trefoil peptide family members, including pS2. Accordingly, Applicants respectfully submit that the specification enables the use of the family of trefoil peptides, including ITF, SP, and pS2.

In sum, the specification adequately enables the treatment of all recited ophthalmic conditions, for the purpose of restoring or maintaining the integrity of the corneal epithelium. Based on Applicants' data demonstrating the effectiveness of ITF and SP, combined with the prior art that showing a commonality of function among trefoil peptide family members, the specification also enables the use of ITF, SP, and pS2, as claimed. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner asserts that the claims do not recite the disease aspects that are positively affected by "treatment." Applicant notes that the preamble of

claims 1 and 7 have been amended to direct the artisan to the specific feature that is the subject of treatment, namely epithelial cell injury. Furthermore, Applicant direct the Examiner's attention to the definition of "treatment of lesions" at page 13, lines 12-19 which specifies treatment to include both the prevention of lesion formation and the healing of existing lesions. In view of these amendments and remarks, Applicant respectfully requests withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102

Claims 1, 2, 6, 7, and 12 are rejected under 35 U.S.C. § 102(b), as being anticipated by Wilson (U.S. Patent No. 5,703,047). The Examiner points out that Wilson teaches corneal epithelial wound healing using hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), epidermal growth factor (EGF), and transforming growth factor alpha (TGFα). The Examiner then asserts that these growth factors fall within the definition of trefoil proteins provided in the specification.

None of the growth factors of Wilson fall within the family of trefoil proteins as defined in the specification. In justifying this rejection, the Examiner has only considered the dependent portion of the trefoil protein definition which, when taken out of context, yields an incorrect interpretation compared to the definition as a whole. In fact, the definition begins by exemplifying ITF, SP and pS2 as trefoil protein family members followed by the statement that "these proteins are designated trefoil proteins because they have a trefoil shaped secondary structure which is stabilized by intrachain disulfide bonds" (page 7, lines 14-17, emphasis added). The growth factors of Wilson do not have a trefoil shaped secondary structure and, therefore, cannot fall within the family of trefoil proteins as defined. Accordingly, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. Enclosed is a petition to extend the period for replying for three months, to and including January 3, 2002. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: January 3, 2002

Paul T. Clark
Reg. No. 30,162

BIEKER-BRADY
Reg No 39,105

Clark & Elbing LLP
176 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

21559
PATENT TRADEMARK OFFICE

\\Clark-w2k1\documents\50206\50206.432001 Reply to OA of 7.3.01.wpd

Version With Markings to Show Changes Made

In the Title:

TREATING EYE DISORDERS USING INTESTINAL TREFOIL PROTEINS

In the Specification:

Page 1, lines 3-10:

This application is a continuation-in-part of U.S.S.N. 08/631,469, filed April 12, 1996, now U.S. Patent No. 6,221,840, which is a continuation-in-part of U.S.S.N. 08/191,352, filed February 2, 1994, now abandoned, which is a continuation of U.S.S.N. 08/037,741, filed March 25, 1993, now abandoned, which is a continuation of U.S.S.N. 07/837,192, filed February 13, 1992, now abandoned, which is a continuation-in-part of U.S.S.N. 07/655,965, filed February 14, 1991, now abandoned.

In the Claims:

1. (Amended) A method for the treatment of an eye disorder in a patient, said disorder characterized by an injury to the corneal epithelial, said method comprising administering to said patient a trefoil protein, or a biologically active fragment thereof.

5. (Amended) The method of claim 2, wherein said trefoil [peptide] protein is pS2.

7. (Amended) A method for the treatment of a[n eye] lesion of the corneal epithelium in a patient, said method comprising administering to said patient a trefoil peptide, or a biologically active fragment thereof.

9. (Amended) The method of claim 7, wherein said trefoil peptide is intestinal trefoil [peptide] factor (ITF).

10. (Amended) The method of claim 7, wherein said trefoil [peptide] protein is spasmolytic peptide (SP).

11. (Amended) The method of claim 7, wherein said trefoil [peptide] protein is pS2.